TITLE OF CASE

Facilitated Subcutaneous Immunoglobulin Treatment in Pemphigus Vulgaris

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SUMMARY

A novel administration strategy of immunoglobulin treatment is represented by injection of recombinant human hyaluronidase (rHUPH20) with subcutaneous immunoglobulins. The use of facilitated subcutaneous Immunoglobulin Treatment (fSCIG) for the treatment of autoimmune

conditions is yet to be investigated.

We present the case of a 56-years old female patient with pemphigus vulgaris predominantly of the oral mucous membranes, previously treated for 24 months with azathioprine and medium-doses of steroids, with only partial remission. When she came to our attention, a concomitant newly diagnosis of infiltrating ductal breast cancerlimited the use of immunosuppressive agents. She was started with fSCIG (25 g/montly). After 18 months of follow-up, her breast cancer has been successfully treated and a substantial decrease of the rate of bullous mucous lesions and improvement of time to lesion healing and resolution was observed.

fSCIG might represent an steroid-sparing tool for the treatment of selected cases of pemphigus vulgaris.

BACKGROUND

Immunoglobulin treatment has been investigated in numerous autoimmune conditions, especially due to their safe profile and simple administration. Indeed, immunoglobulin treatment is particularly appealing when the use of other immunosuppressive strategies is limited due to concomitant conditions, such infection or malignancy [1][2].

A novel administration strategy of immunoglobulin treatment is represented by injection of recombinant human hyaluronidase (rHUPH20) with subcutaneous immunogobulins (SCIG) that facilitate SCIG treatment (fSCIG). This enzyme facilitates drug dispersion and absorption by increasing the hydraulic conductivity in the interstitium. Therefore, fSCIG have the advantages of having the possibility of higher IgG injection rates, bioavailability and increased infusion volumes [3]. rHUPH20 is short acting, with a short half life (<30 minutes), which entails a prompt tissue restoration (24-48h) [4]. In addition, rHUPH20 induces only modest immunogenicity which has no association with adverse events [5].

fSCIG treatment presents many advantages for patients that undergo immunoglobulin therapy. Compared to intravenous immunoglobulins (IVIG), fSCIG can be a self-injected at home, improving the quality of life of the patients. Furthermore, considering IVIG, the rate of systemic adverse reactions is significantly lower [5]. When comparing SCIG treatment alone, fSCIG are injected less frequently (1-2 weeks vs monthly infusions), in a single site with an overall better bioavailability, higher IgG injection rates and increased injection volumes.

The use of Immunoglobulin therapy for autoimmune conditions has been proven and analyzed in numerous trials [6], however, the potential use of fSCIG has yet to be investigated. We hereby present a case of a patient with pemphigus vulgaris treated in our center with fSCIG.

CASE PRESENTATION

We present the case of a 56 years old female patient with biopsy proven pemphigus vulgaris predominantly of the oral mucous membranes (Anti-Desmoglein D1 0,85 U/ml and Anti-Desmoglein D3 145,4 U/ml).

After the diagnosis in 2015, the patient has been treated over the years with oral steroids (25 to 12.5 mg prednisone daily) and azathioprine (50-100 mg daily), with only partial response.

When she came to our attention, the patient presented with a concomitant newly diagnosis of infiltrating ductal breast cancer and she was on 12.5mg corticosteroids daily. She successfully underwent excision surgery with axillary lymph node biopsy and radiotherapy. Taking into account the clinical and biological features of the lesion, treatment with tamoxifene 20 mg (1 cp / day) associated with GnRh analogue treatment was started.

While undergoing the treatment for the malignancy, the patient experienced a considerable worsening of the autoimmune condition, with increased rate of bullous lesion and duration, while on solely steroid treatment.

INVESTIGATIONS

The undergone relevant investigation are resumed in Table 1.

DIFFERENTIAL DIAGNOSIS

Differential diagnosis included Paraneoplastic Pemphigus, which is a rare autoimmune mucocutaneous blistering disease associated with an underlying malignancy. It is thought to be caused by antibodies to tumor antigenscross-reacting with epithelial antigens, specifically desmosomal and hemidesmosomal antigens [7].

TREATMENT

Due to the concomitant diagnosis of infiltrating breast cancer, the immunosuppressive therapy was suspended. Possible available therapeutic options were screened, including anti-CD20 B-cell depletion therapy, to date considered a therapy of choice in similar cases. However, due to the history of malignancies and to address the specific request of the patient to drastically reduce her hospitalization time, she was started with fSCIG (25 g; 0.36g/kg/month) at monthly cycles, in one injection. After initially trained at our centre, the patient began to undergo home-based monthly therapeutic

cycles.

The patient was closely follow-up with monthly clinical and laboratory monitoring

OUTCOME AND FOLLOW-UP

The patient was follow-up for 18 months, with substantial decrease of the rate of bullous mucous lesions: the rate of lesions decreased from one new weekly lesion to one every three weeks. There was also an improvement of time to lesion healing and resolution: one week to ten days with sole steroid therapy v.s. three to four days with fSCIG.

Figure 1 illustrates the resolution of a bullous lesion within just 2 days.

After four months, steroid treatment was tapered down during the course of two months, down to 7,5 mg of corticosteroids. Of note, before starting the therapy with fSCIG, she has never been able to taper her prednisone dose below 12.5 mg daily due to the frequency of her oral lesions.

DISCUSSION

Pemphigus vulgaris is a rare and life-threatening disease and patients suffer from a debilitating quality of life[8]. The treatment goal in patients with pemphigus vulgaris is to induce and maintain remission, which clinically

corresponds to cessation of new blister formation, healing of old wounds and to eventually complete the tapering of steroid treatment [9].

Recently, Wasserman et al in a phase III study [10] and in its extension study [11] demonstrated that fSCIG have equivalent efficacy, safety profile and overall pharmacokinetic to IVIG. Of note, the most common adverse reaction in patients that underwent fSCIG treatment was local reaction in the injection site, with a similar rate to SCIG. In contrast, fSCIG injections had a significant lower rate of systemic reactions compared to the IVIG[11]. During the extension study the frequency of systemic adverse reactions remained low and the rate of relater local adverse reactions decreased from 3.68/subject-year in months 1-12 to approximately 1.50/subject-year after 30 months of treatment. When comparing the pharmacokinetic profiles between the different infusion methods, fSCIG and IVIG had similar serum through levels, with a median of 10 g/L and 10,4 g/L, respectively. Peak serum IgG levels were lower after fSCIG than after IVIG. Higher peak serum IgG levels might be responsible of the different systemic reaction rate between the two methods [12]. In addition, when comparing SCIG alone, fSCIG improved the drug bioavailability by approximately 20%. Figure 2 illustrates the pharmacokinetics of the IgG serum

levels different routes of administration of immunoglobulin replacement therapy.

IVIG has been proven as efficacious for various autoimmune diseases and has been proposed to be a promising toll for the management of selected cases of pemphigus vulgaris[13]. The advantages of immunoglobulin therapy are relatively safe drug profile, especially important in the case presented, and ease of delivery, with only a single cycle per month.

Due to the lack of available experience related to the use of fSCIG for immunomodualtory purpose, we applied the conventional protocol used for fSCIG as a replacement therapy in patients with hypogammaglobulinemia.

fSCIG might further improve patient care, with home self-injections and significantly lower rate of systemic adverse reactions and might represent an important tool for the treatment of selected pemphigus vulgaris patients. Future studies will be needed to investigate fSCID infusion regimens (dosage and schedule) tailored for autoimmune conditions.

LEARNING POINTS/TAKE HOME MESSAGES

1- The use of immunoglobulin therapy for autoimmune conditions has been

proven and analyzed in numerous studies, but the use of fSCIG is yet to be investigated.

2- We present the case of a patient with pemphigus vulgaris treated with fSCIG(25g) at monthly cycles with substantial decrease of the rate of bullous mucous lesions and improvement of time to lesion healing and resolution.

3- fSCIG might further improve patient care, with home self-injections and significantly lower rate of systemic adverse reactions and might represent an important tool for the treatment of selected pemphigus vulgaris patients.

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FIGURE/VIDEO CAPTIONS

Figure 1.*Resolution of a bullous oral lesion within two days.*

Figure 2. *Pharmacokinetics of the IgG serum levels different routes of administration of immunoglobulin replacement therapy. Adapted from Wasserman et al [6].*

Tables

Table 1. *Investigations undergone by the patient*

Blood count	WBC 5740 (cells/µl), Neutrophils 4700/µl, Lymphocytes 780/µl, Monocytes 25/µl, Eosinophils50/µl, Basophiles 40/µl, RBC 4,83X10^6/µl, Hb12.6 g/dl, MCV 81fL, PLTs 321000/µl
Blood tests	Immunoglobulins: IgG 1080/IgM 71/IgA 187, C3 68 mg/dl, C4 7 mg/dl ANA neg, anti dsDNAneg, ANCA neg, cryoglobulinsneg, antiphospholipid antibodies neg, rheumatoid factor 472 HBV-DNA: neg; HCV-RNA: neg; normal complete urine test.
Oral Mucosa biopsy	Epithelium with cracks in deeper layers of malignant, acantolytic keratinocytes. Stroma slightly emaciated with small pervascular infiltrative lymphoestiocytic nodes. Direct Immunofluorescence: intracellular IgG +++, C3 to intercellular fluorescence +.
Breast Cancer Histology	Infiltrating ductal carcinoma, G2, maximum size 16 mm, lymphocyte invasion, MTS free sentinel lymph node, pT1c, pNo. ER 99%, Prg 99%, Ki67 31%, HER2 score O.
Abdominal	Unremarkable

echography	
Chest radiography	Unremarkable